05BioST01 Introduction to Study Designs and Clinical Trials

Biostatistics
Common Study Design

林　建　甫
C.F. Jeff Lin, MD. PhD.

台北大學統計系助理教授
台北榮民總醫院生物統計顧問
美國密西根大學生物統計博士

Descriptive Studies

- Case reports
- Case series
- Population studies

Descriptive Studies: Uses

- Hypothesis generating
- Suggesting associations

Analytical Studies

- Observational
- Experimental

Observational Studies

- Cross-sectional
- Case-control
- Cohort

Types of Studies Classified by Temporal Point of View

I. Instantaneous Studies - **Surveys**

- **II.** Longitudinal Studies
  - **A.** Retrospective Studies
    - **Historical Observational Cohort**
    - **Case - Control**
  - **B.** Prospective Studies
    - **Prospective Observational Cohort**
    - **Clinical Trial**
  - **C. Hybrid Designs**

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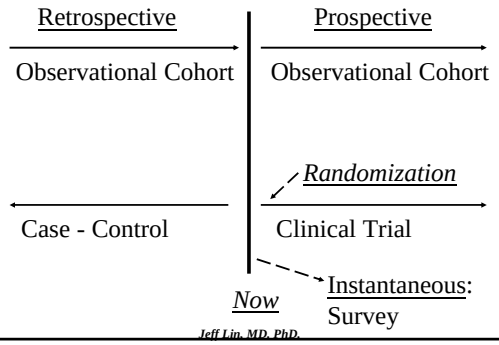
A Schematic for Temporal Classification



Study Designs

Three different common study designs:

- Cross-Sectional (surveys)
- Case-Control (retrospective)
- Cohort (prospective – clinical trial)

Eat Garlic

- Garlic is the key to good health
- Be sure to eat garlic with every meal
- Garlic-it's heart healthy

Garlic is wonderful

I. Instantaneous: Population-Based Studies

- Synonyms
  - **Survey**
  - Population-Correlation Study
  - Ecological Study
- Two or more populations are *instantaneously* compared through the prevalences of both exposure and disease.
- As summarized units get smaller (country → region → neighborhood → individual), a survey approaches a historical observational cohort study.

Cross-Sectional Design

- Cross-sectional designs take a single sample (often a survey) at a specific time.
- Cross-sectional designs are used to establish relationships between two variables
- Cross-sectional designs are inexpensive and quick

Cross-sectional Study

- Data collected at a single point in time
- Describes associations
- Prevalence

A "Snapshot"

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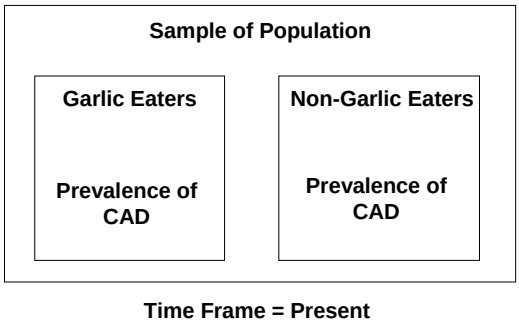
Prevalence vs. Incidence

- Prevalence
  - The total number of cases at a point in time
  - Includes both new and old cases
- Incidence
  - The number of new cases over time

Cross-sectional Study



Time Frame = Present

Cross-sectional Study

Garlic Consumption

CAD	+	-
+	10	90
-	90	10

Example of a Cross-Sectional Study

Association between garlic consumption

and CAD in the Family Practice Clinic

Cross-Sectional Study

- Strengths
  - Quick
  - Cheap
- Weaknesses
  - Cannot establish cause-effect

Case-Control Studies: Weaknesses

- Cannot measure
  - Incidence
  - Prevalence
  - Relative Risk
- Can only study one outcome
- High susceptibility to bias

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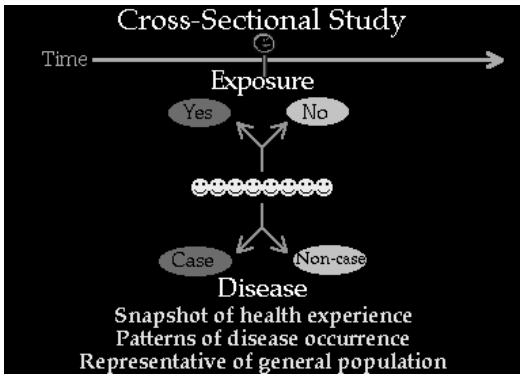
Cross-Sectional Design

- Objective: To establish a relationship between two variables, when both are binary.
- Focus: Not on a particular variable.
- Timing: Present. Take one sample and cross-classify.
- Drawback: If either variable/factor is rare you will lack information on the relationship under investigation.
- Benefit: inexpensive, used for hypothesis generation.



Tennis Elbow Survey

- Members of several tennis clubs in the Boston area were surveyed.
- Participants was asked how many episodes
- Enroll roughly an equal number with at least one episode of tennis elbow (the cases) and subjects with no episode of tennis elbow (the controls).
- Possibly related factors, including demographic factors (e.g., age, sex) and characteristics of their tennis racquet (string type of racquet used, materials of racquet).

Tennis Elbow Survey

Table 1.1: Some of tennis elbow survey data

Id	Age	Sex	Numepis	Typlast	WgtLast	Matlast	Strlast	Typcurr	Wgtcurr	Matcurr	Strcurr
1	53	1	3	1	3	5	2	1	3	5	2
2	57	1	3	1	3	1	1	2	2	2	1
3	43	1	1	1	2	2	1	1	2	4	1
4	35	2	2	1	3	3	2	1	3	3	2
5	43	1	2	1	3	2	2	1	3	2	2
6	31	1	1	1	3	4	2	1	3	4	2
7	36	1	1	1	2	1	2	1	2	1	2
8	36	2	1	2	3	2	2	2	3	2	2
9	33	2	1	1	2	5	1	1	2	1	1
10	34	1	3	9	3	1	2	1	3	1	2
						...					

II. Longitudinal: Individual-Based Studies

- A longitudinal study observes exposures and events for individuals **over a period of time**.
- There are two types, depending on whether one is looking forwards (***prospective)*** or backwards ***(retrospective)*** from the present.

Longitudinal Studies: A. Retrospective

- **Historical Observational Cohort**
  - **Synonyms -** survey, retrospective cohort study.
  - Examines outcomes among patients with past exposures.
  - E.g., track down 1950s asbestos miners & determine current status.
- **Case - Control** (Breslow and Day, 1980)
  - **Synonyms -** case referent, retrospective study.
  - Examines past exposures among a group of patients with current outcomes.
  - E.g., interview mesothelioma patients & determine past exposures.

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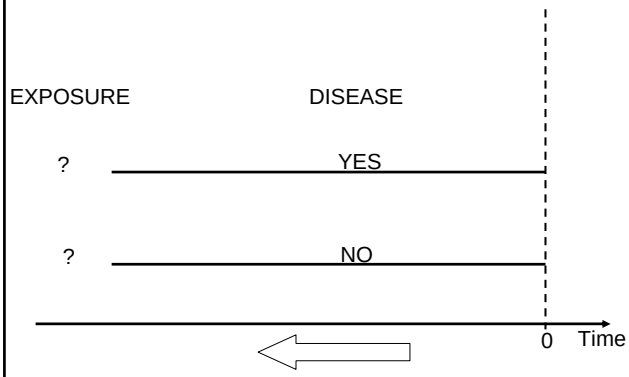
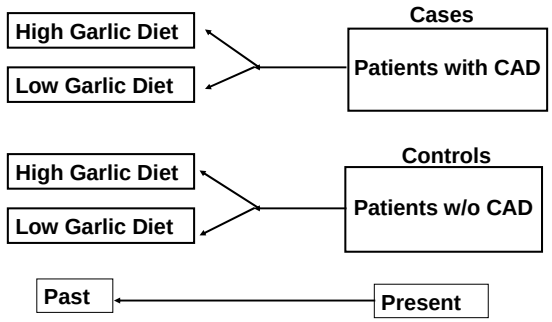
Case-Control Design

- Case-control studies are ***retrospective*** because exposure data is based on ***recall*** of past exposure.
- Retrospective study with a pre-specified number of cases (those with disease) and controls (those without disease). Both cases and controls are surveyed regarding their past exposure to a suspected risk factor.

Case-Control Study



Case-Control Study



Example of a Case-Control Study

Are those with CAD less likely to have consumed garlic?

Case-Control Studies: Strengths

- Good for rare outcomes: cancer
- Can examine many exposures
- Useful to generate hypothesis
- Fast
- Cheap
- Provides Odds Ratio

Case-Control Design

- Objective: To determine a relationship, if any, between disease and exposure.
- Focus: A particular disease
- Timing: Selection of cases and controls is in the present. Data regarding exposure is collected retrospectively.
- Drawback: Inaccuracy of exposure history. Questionable cause-effect implication (timing). Selection of appropriate controls.
- Advantages: Provides adequate number of cases even for rare diseases. Economical and quick.

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Passive Smoking and Lung Cancer

- A group of 518 cancer cases ages 15-59 and a group of 518 age- and sex-matched controls by mail questionnaire
- Main purpose is to assess the effect of passive smoking on cancer risk

Passive Smoking and Lung Cancer

Table 1.5: Relationship of passive to cancer risk

	Passive smoker		
Status	Yes	No	Total
Case	281	228	509
Control	210	279	489
Total	491	507	998

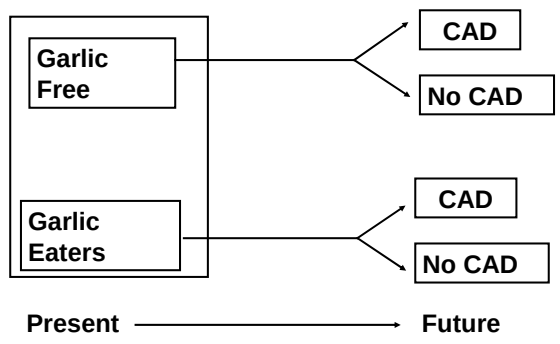
Prospective Studies

- **Prospective Observational Cohort**
  - **Synonyms -** prospective trial, 'clinical trial'.
  - No intervention.
- **Randomized Controlled Clinical Trial**
  - **Synonyms -** prospective interventional cohort study, experiment, prospective trial, clinical trial.
  - Experimenters directly intervene in patient treatment, usually on a randomized basis with controls.

Cohort Design

- Cohort studies are ***prospective*** because they follow a group (cohort) ***over time*** to determine disease status.
- Enroll one or several groups with different exposure status (example: non-smokers and smokers)
- The outcome is occurrence of an event (example: death, cancer)

Prospective Cohort Study



Example of a Cohort Study

To see the effects of garlic use on CAD mortality in a population

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Cohort Study: Strengths

- Provides incidence data
- Establishes time sequence for causality
- Eliminates recall bias
- Allows for accurate measurement of exposure variables

Cohort Study: Strengths

- Can measure multiple outcomes
- Can adjust for confounding variables
- Can calculate relative risk

Cohort Study: Weaknesses

- Expensive
- Time consuming
- Cannot study rare outcomes
- Confounding variables

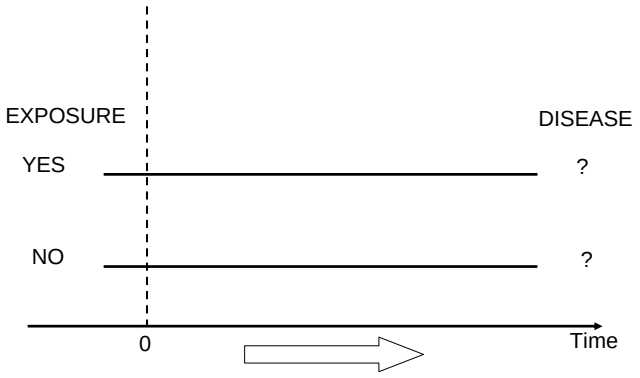
Cohort Study: Weaknesses

- Exposure may change over time
- Disease may have a long pre-clinical phase
- Attrition of study population

Cohort Design

- Objective: To investigate the relationship between exposure and future outcome.
- Focus: a particular exposure
- Timing: Sampling takes place in the present, but primary data are future occurrences of the outcome in exposed vs. non-exposed cohort members.
- Drawback: Time-consuming and costly
- Advantages: adjust for confounders, time-exposure relationship evident.

Prospective Cohort Study



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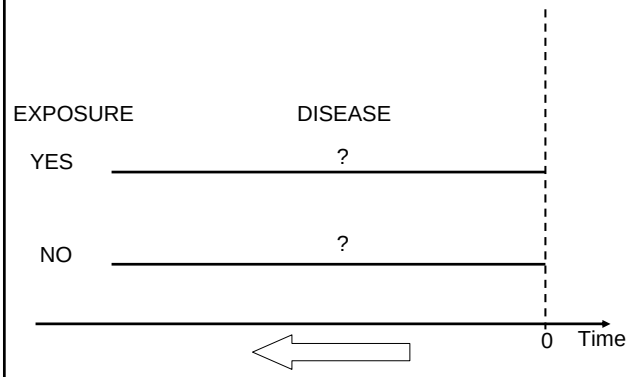
Retrospective Cohort Study



Drinking and Lung Cancer

- Drinking status of 4000 subjects is determined at baseline and the subjects are followed for 10 years to determine cancer endpoints.
- Heavy dringking: $\geqq$ 2 drink per day

Drinking and Lung Cancer

Table 1.6: Crude relationship between lung-cancer incidence and drinking status

	Lung cancer		
Drinking status	Yes	No	Total
Heavy drinker	33	1667	1700
Nondrinker	27	2273	2300
Total	60	3940	4000

Clinical Trials: A subgroup of cohort design.

- Patients are randomized to receive one of two or several treatments.
- Patients are followed over time to determine outcome status.
- Comparison's are made between treatment groups

What is a Clinical trial?

- A ***clinical trial*** is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings.

Clinical Trials

- Patients are randomized to receive one of two or several treatments.
- Patients are followed over time to determine outcome status.
- Comparison's are made between treatment groups

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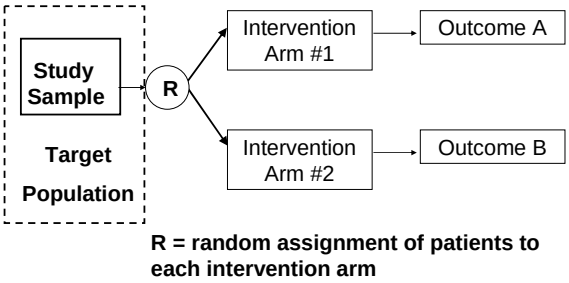
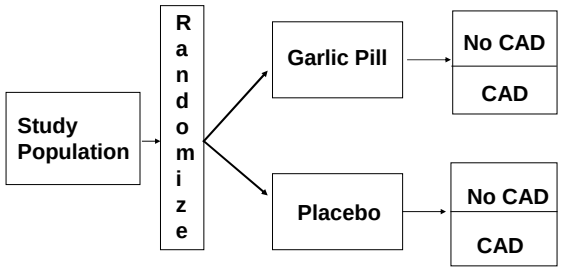
Structure of a Simple, Randomized Clinical Trial



R = random assignment of patients to each intervention arm

Clinical Trial



Clinical Trials

Strengths:

- Best measure of causal relationship
- Best design for controlling bias
- Can measure multiple outcomes

Weaknesses:

- High cost
- Ethical issues may be a problem
- Compliance

Clinical Trials

- Objective: Determine if patients have different outcomes based on treatments.
- Focus: Treatment and Outcome
- Timing: Future. Patients randomized into groups and followed over time.
- Drawback: Time consuming and expensive.
- Advantages: Most scientifically sound method to determine effectiveness of a treatment in a public health setting.

Clinical Trial: An Example

- The remission time of 42 patients with acute leukemia were reported from a clinical trial undertaken to assess the ability of the drug 6-mercaptopurin (6-MP) to maintain remission.
- Each patient was randomized to receive either 6-MP or placebo.

Clinical Trial: An Example

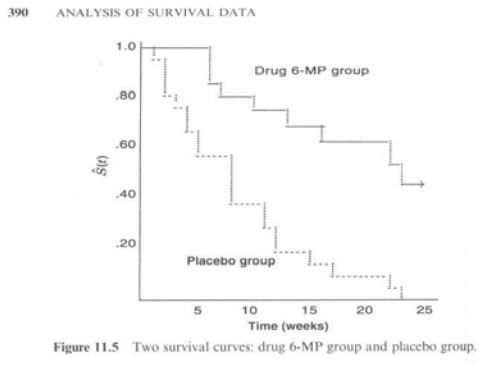


Figure 11.5 Two survival curves: drug 6-MP group and placebo group.

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Definitions:

- Units: individuals on which the expriment is done.
- Treatment: The experimental condition applied to the units.
- Factors: explanatory variables in an experiment (includes treatment).
- Level: A specific combination of factors if an experiment contains more than one factor.

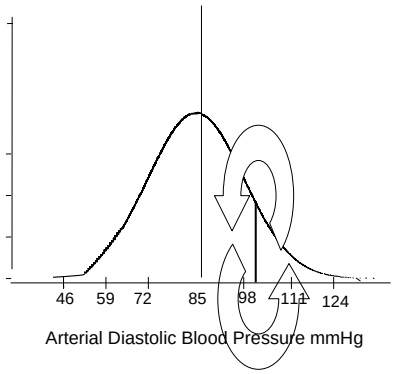
Definitions for clinical trials:

- Placebo: A dummy pill which looks and tastes the same as the actual treatment.
- Placebo effect (halo effect): When subjects respond favorably to a placebo pill. (Positive outcome may be due to change in behavior with receiving any treatment, expectations of a cure, or regression towards the mean).

Regression to the Mean: An Example

- An internal medicine doctor wanted to test a new drug for lowering blood pressure.
- He chose patients with one reading of high blood pressure to participate in his study, since he felt these patients were in a greater need for treatment.
- After three months of prescribing the drug to these patients, he measured their blood pressure again and declared it was effective!

Regression Towards the Mean



Regression to the Mean: An Example

- The patient was chosen to participate in the study because his blood pressure was at a high value.
- The improvement in blood pressure for the group may be due to other factors such as:
  - Weight loss
  - Exercise
  - Reducing Stress
  - Cutting sodium intake

Definitions for clinical trials

- Bias: The design of an experiment is biased if it systematically favors certain outcomes.
- Control group: Subjects who receive placebo or no treatment instead of treatment.
- (Active control group: current standard treatment)
- Randomization: The use of chance to divide experimental units into groups.
- Double –blind: neither the subjects nor the medical personnel who work with the them know which treatment any subject has received.

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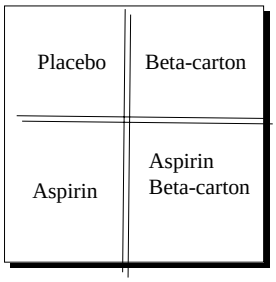
Physicians' Health Study: An Example

- Does regularly taking aspirin help protect people against heart attack?
- Study looked at the effect of two drugs: aspirin and beta carotene.
- 21,996 male physicians randomized into 4 groups and followed for several years.
- Odd numbered days subjects took aspirin or aspirin placebo.
- Even numbered days subjects took beta carotene or beta carotene placebo.

Physician's Heath Study



Aspirin vs. no Aspirin

Beta-carton vs. no Beta-carton

Physicians' Health Study

- Experimental Units: Physicians
- Treatments: Aspirin and Beta Carotene
- Levels:
  1. Aspirin and Beta Carotene
  2. Aspirin and Beta Carotene Placebo
  3. Aspirin Placebo and Beta Carotene
  4. Aspirin Placebo and Beta Carotene Placebo
- Response Variable: Heart attack, cancer, other medical outcomes

Physicians' Health Study

- Outcomes for Aspirin:

  239 of placebo group had suffered heart attacks

  139 of aspirin group had suffered heart attacks
- Outcomes for Beta Carotene

  There wasn't a significant difference in cancer rates for the placebo vs. the beta carotene groups.

Significant Difference

Significant difference: the observed effect is so large it would rarely occur by chance.

The heart attack rate in the placebo group was significantly different than the heart attack rate in the aspirin group. Aspirin appears to be protective against heart attack.

Minimizing Variation in a Clinical Trial

1. Including a control (reference) group1
2. Randomly assigning patient to treatment groups or experimental conditions.
3. Restricting patients who enroll in a study to reduce variation between patients.
4. Blinding patients, investigators etc.
5. Forming blocks of experimental units (pair matching).

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Controlled Clinic Trial

- Controlled clinical trials compare one treatment against another treatment (often standard of care).
- This ***comparative study*** approach allows investigators to separate treatment effects from other factors (such as normal biologic variation, regression to the mean).

Randomization

Randomization: the use of chance to divide experimental units into groups.

Random assignment of patients to treatment groups or conditions minimizes extraneous variation by helping to ensure that all patients who enroll in the study have an equal chance of receiving treatment

Randomization

Why?

- If one group is sicker, older, smarter or anything systematically different we cannot trust our outcome is not due to these variables. Randomization spreads these variables between groups in a non-systematic way.
- If we try to systematically match people we could miss important lurking variables.
- If we allow physicians to choose treatments during a trial, they often will give the treatment to the sicker patients in hopes it will help them – then the outcome is biased against treatment.

Randomization guarantees that statistical tests will have the valid significance levels.

Blinding

1) of patient
2) of treatment team
3) of endpoint assessment
4) committee monitoring response variables

Blinding of Treatments

Non-blind	- Investigator and patient know treatment assigned
Single-blind	- Investigator knows treatment assigned but patient does not
Double-blind	- Neither investigator nor patient knows treatment assigned
Triple-blind	- Double-blind + blind to the committee monitoring response variable
General view	- Double-blind > single blind > non-blind

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Restriction of Enrollment Inclusions/Exclusions

- Restricting enrollment to a particular population can help to reduce variation among participants.
- Be careful not to generalize results outside of the population under study.

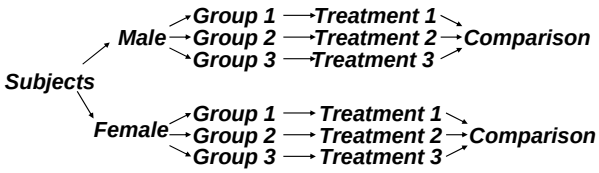
Block Design or Stratification

Matching subjects that are known before the experiment to be similar in some way that is expected to affect the response to treatments. (pair matching)

Some typical examples:

1. Gender
2. Smokers vs. Non-smokers
3. Age groups

Block Design or Stratification



Warning: Do not make comparisons between blocks!

Statistical Design: Basic Principles

1. Control – control the effects of lurking variables on the response, most simply by comparing two or more treatments.
2. Randomization – use impersonal chance to assign experimental units to treatments.
3. Blinding – eliminate bias associated with physician/patient being aware of treatment that is given.
4. Inclusion and Exclusions – reduce heterogenesity.
5. Replication – replicate each treatment on many units to reduce chance variation in the results.

Phase I Trials

- Definition - Dose-finding and safety
- Goals
  - Establishes safe maximum tolerated dose, appropriate dosing schedule, and may compare formulations
  - Provides limited data on pharmacology, toxicity, effects
- Size -20-50 persons at a single site
- Study Populations - subjects may be healthy, have the targeted disease, or be terminal with unrelated disease
- Design - Dose escalation in groups of patients

Phase II Trials

- Definition - Efficacy (any effect ?) and optimal dose
- Goals - determine treatment effects and toxicity
  - Selects optimal dose for Phase III studies
  - Provides more complete information on pharmacokinetics
- Size - 50 – 300 patients
- Study Populations - patients with the targeted disease at 1 - 4 sites
- Design - sometimes comparative and if so:
  - may be randomized to compare test drug to placebo or other drugs or among several doses of test drug
  - analysis is “as treated”

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Phase III Trials

- Definition - provides basis for licensing of drugs or devises
- Goals - determines effectiveness and safety in settings that simulate actual medical practise
- Size - 200-1000 patients
- Study Populations - patients with the targeted disease at multiple geographical sites
- Design - always comparative, randomized, blinded
  - a single primary outcomes is defined
  - analysis must be by "intent to treat," all randomized patients must be included in analysis

Phase IV Trials

- Definition - "post marketing" after drugs released for general use
- Goals / Design -
  - phase II or III trials of the drug or device in unstudied populations (children, pregnant women, person with second diseases)
  - active or passive surveillance to detect rare side effects in large numbers of patients

Thanks !